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(54) Title: FOAMABLE FORMULATION AND FOAM (57) Abstract There is described a formulation comprising a foamable gelling agent (such as alginate, carageenan or carboxymethylcellulose gels) and a slow-release precipitant therefor. The precipitant is combined with the gelling agent during foaming and stabilises the foamed form of the gelling agent. Suitable precipitants include calcium salts such as calcium citrate and calcium chloride, or aluminium salts such as aluminium chloride. The increased stability of the foam facilitates sterilisation thereof. Further improvements can be obtained by exposing the cured foam to a precipitant applied externally, optionally washing, and then drying the foam. The foam of the present invention is suitable for medical or veterinary use and can include active ingredients for delivery to, for example, a wound site.		

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1 FOAMABLE FORMULATION AND FOAM

2

3 The present invention is concerned with a foamable
4 formulation and the foam formed therefrom.

5

6 A wide variety of gels, creams, ointments, lotions and
7 other formulations are available for application to a
8 body surface. The exact content of these compositions
9 will vary depending upon the purpose of application.
10 For example, a formulation may be applied to clean a
11 body surface, to promote healing of any wound or
12 injury, to prevent an exposed wound on the body from
13 drying out, to prevent infection, etc. In certain
14 circumstances the composition may include an active
15 ingredient.

16

17 In our International Patent Application published 13
18 June 1996 under No WO-A-96/17595 we describe a foamable
19 formulation which comprises a foamable carrier or
20 gelling agent, for example an alginate gel, and an
21 active ingredient, such as a water soluble glass
22 powder.

23

24 The product described in WO-A-96/17595 represented a
25 considerable advance over the use of gel or cream.

1 We have now found that by including a precipitant for
2 the gelling agent, in a slow-release form within the
3 composition, further improvements with regard to the
4 setting time of the foam and its stability can be
5 achieved. In particular, the added stability enables a
6 pre-foamed pad to be sterilised by irradiation,
7 ethylene oxide, or other conventional means.

8
9 Thus, the present invention provides a formulation
10 comprising a foamed gelling agent combined with a slow-
11 release precipitant therefor. The gelling agent may be
12 any agent capable of forming a foam, although
13 preferably the gelling agent is physiologically
14 compatible and non-irritant when maintained in contact
15 with the body surface. The gelling agent may be a gel,
16 for example a sodium alginate gel, carageenan gel,
17 sodium carboxymethylcellulose gel or mixtures thereof.

18
19 The precipitant is desirably intimately admixed
20 throughout the whole of the foamed gelling agent,
21 preferably during the foaming process. In certain
22 circumstances however the presence of the precipitant
23 on one surface of the foamed gelling agent may be
24 sufficient to cause stabilisation of the foam.
25 Examples of precipitants include stabilising
26 crosslinking agents which render the gelling agent
27 insoluble. Examples include salts of polyvalent metal
28 ions such as calcium, zinc, copper, silver or aluminium
29 as well as borates, glyoxal and amino-formaldehyde
30 precondensates. In one embodiment, the polyvalent
31 metal ion may be released from a water-soluble glass
32 which is admixed into the foamable carrier in
33 comminuted form. A copper ion-releasing water soluble
34 glass, a zinc-ion releasing water soluble glass and
35 mixtures thereof are particularly of interest.

36

1 The role of the precipitant is to stabilise the foamed
2 gel so that a stable foam is produced. Generally, the
3 stable foam should be produced within a reasonable time
4 period since if the precipitant is too slow-acting, the
5 foam structure will have collapsed prior to
6 stabilisation. However, a very fast acting precipitant
7 may not allow sufficient time for the gel to be foamed.
8 Desirably, the precipitant stabilises the foamed gel
9 over a time period of 1 minute to 120 minutes,
10 preferably within 30 minutes, and most preferably
11 within 15 minutes at ambient temperature. The foam is
12 considered to be "cured" when it can be lifted and
13 carefully handled without collapse. The solubility of
14 the precipitant and hence the setting (cure) time of
15 the foam may be varied by adjusting the pH of the
16 composition, especially where the precipitant is based
17 upon a calcium salt. Generally, the solubility of a
18 calcium salt will be increased by lowering the pH.
19 Typical pH adjusters include organic acids such as
20 acetic, adipic, citric, fumaric, lactic, alginic and
21 tartaric acids. Usually an amount of 0.5 g to 5 g of
22 organic acid per 100 gel is sufficient. The organic
23 acid may be admixed with the precipitant prior to
24 foaming or, more preferably, may be admixed with the
25 gelling agent prior to foaming.

26
27 Suitable precipitants include calcium citrate, calcium
28 carbonate, calcium phosphate, calcium hydrogen
29 phosphate (CaHPO_4), aluminium chloride, barium
30 carbonate, barium phosphate, barium sulphate, barium
31 chloride and zinc carbonate.

32
33 Where the gelling agent comprises an alginate gel, a
34 carageenan gel or a carboxymethylcellulose gel one
35 preferred precipitant is a calcium salt. Whilst
36 calcium citrate has been used in the examples, other

1 slowly dissolving calcium salts are also suitable.

2

3 Where the gelling agent comprises
4 carboxymethylcellulose gel one preferred precipitant is
5 an aluminium salt.

6

7 In one embodiment the gelling agent and precipitant are
8 packaged separately and only admixed during the foaming
9 process or subsequent to foaming.

10

11 Alternatively, the precipitant may be included in a
12 suspension (e.g. a suspension of calcium citrate and
13 glycerine) which forms a separate layer on top of the
14 gelling agent which remains substantially inert during
15 handling and/or storage. Only once the operator
16 desires to produce the foam, is the precipitant
17 intimately admixed with the gelling agent (for example
18 by shaking the container) and then promptly foamed.
19 Using the precipitant in suspension form has the
20 benefit that the suspension is easier to dispense from
21 a pressurised container than a powder and also provides
22 for more accurate dosing of unit precipitant per unit
23 gelling agent.

24

25 Optionally, the formulation may comprise other
26 additives such as decompactants which promote the
27 desired foam structure or other foaming agents,
28 plasticisers, humectants, preservatives, additives,
29 sequestering agents or active ingredients such as
30 antimicrobial agents, growth factors, hormones, living
31 cells, etc.

32

33 The foam may be applied directly to the body area and
34 allowed to produce a stable foam protective cover, for
35 example over a wound. With the addition of the
36 precipitants the cure of the foam is significantly

1 reduced, rendering the product more user friendly.

2

3 Alternatively, the foam can be produced onto a mould or
4 other surface area, allowed to cure (for example by air
5 drying or oven drying) and then applied to the body
6 surface as a dressing. A foam sheet of this type is a
7 preferred embodiment of the invention since it exhibits
8 sufficient stability for easy handling whilst retaining
9 a moist surface to promote wound healing. Optionally,
10 the foam may be applied about a substrate (for example
11 cloth, mesh, non-woven pad of alginate fibres, nylon,
12 rayon, polylactid acid, polyglycolic acid,
13 polycaprolactone or biocompatible glass fibres) which
14 are then integrated into the foam pad produced.

15

16 As an example, the foam may be used to treat
17 dermatological conditions (including psoriasis, atopic
18 and allergic eczema). It may be convenient in this
19 embodiment for the foam to deliver an active ingredient
20 normally used to alleviate such conditions, for example
21 a steroid such as hydrocortisone.

22

23 In another embodiment the foam may be used to treat
24 burns or scalds, including sunburn.

25

26 In another embodiment the foam may be applied
27 cosmetically, and for example may include skin
28 moisturising agents, nutritional agents and growth
29 factors suitable to promote skin regeneration. A foam
30 intended for cosmetic use may include colorants or
31 pigments so that the foam may be applied to the skin as
32 a cosmetic or to disguise any blemishes in the skin.

33

34 The foam may be used prophylactically. In particular a
35 foam containing a UV blocking agent may be applied to
36 exposed areas of the skin to protect it from the

1 effects of the sun.

2

3 The formulation of the invention is applied to the body
4 site of interest in the form of a foam and it is
5 therefore essential that the composition undergoes a
6 foaming process before application to the body. In the
7 foaming process gas is forced into or is formed within
8 the formulation to entrap small bubbles of gas therein,
9 thereby forming the foam. Any suitably gas or gas
10 producing system can be used to produce the foam.

11 Mention may be made of butane and nitrous oxide, but
12 other gases like air, nitrogen, hydrofluorocarbons such
13 as HFC134a or 227, hydrocarbons like propane,
14 isopropane or a mixture thereof, are also suitable.
15 Conveniently the foam may be produced by conventional
16 means such as by using aerosol technology.

17

18 The formulation according to the present invention may
19 be stored in any convenient container until required.
20 Generally, the container will be designed to preserve
21 the sterile nature of the formulation. Conveniently
22 the container will be provided with means to foam the
23 composition when required. Details are given in WO-A-
24 96/17595. A two can packaging and dispensing system,
25 as described in our co-pending UK Patent Application No
26 9823029.5 (a copy of which is filed herewith), may be
27 used to dispense the foam according to the present
28 invention.

29

30 Generally, the foam will be produced from sterile
31 ingredients.

32

33 Prior to the foaming process, the foamable carrier is
34 preferably in the form of a gel. The gel may be
35 sterilised and this is generally desirable where the
36 foam is intended for medical use. Usually,

1 sterilisation will take place by autoclaving the
2 formulation, since this is currently the most economic
3 means of achieving sterilisation. Autoclaving at
4 temperatures of from 100°C to 125°C for under ½ hour is
5 normally sufficient. Generally, the autoclaving
6 process should be as mild as possible, whilst being
7 sufficient to sterilise the formulation. For example,
8 autoclaving at temperatures of about 121°C for 15-20
9 minutes is acceptable. The autoclaved formulation may
10 then be foamed when cool. It is also possible,
11 however, to sterilise the formulation by other means,
12 for example by γ -irradiation or e-beam irradiation. It
13 has been found that autoclaving the gel may cause the
14 MW of the foamable carrier to be slightly reduced.
15 Consequently it may be desirable to select a foamable
16 carrier having a higher MW than that ultimately
17 required.

18

19 The foam forms an air-tight cover around any wound or
20 injury to which it is applied, and this prevents that
21 area from drying out and may also combat infection.
22 The advantages of applying a topical product in the
23 form of a foam include:

24

- 25 1. Easy rapid application,
- 26 2. Conforms to surface irregularities,
- 27 3. Insulates the wound,
- 28 4. Cools the tissues,
- 29 5. Offers antibacterial action to prevent
- 30 infection,
- 31 6. Biocompatibility with tissue,
- 32 7. Suitable for use as a vehicle for the
- 33 administration of pharmaceutical agents,
- 34 and/or
- 35 8. Maintains a moist environment.

36

1 Generally, the formulation of the present invention
2 will be applied directly to the body site of interest
3 in the form of a foam, the foam being produced from any
4 suitable device (such as an aerosol) immediately before
5 application. It is, however, possible for a quantity
6 of the foamed formulation to be produced and then
7 applied onto the body site by any suitable means, for
8 example by hand or by spatula. This method may be
9 required for wounds having a narrow opening.

10
11 As stated above, the foam may also be produced on a
12 suitable surface and then allowed to dry to produce a
13 stable foam sheet which can be handled as described (
14 above without deterioration. Generally, the production
15 of the sheet will take place under sterile conditions
16 or may be sterilised after production. In the prior
17 described foam product of WO-A-96/17595, it was not
18 possible to provide a foamed pad product and then
19 sterilise the pad by conventional means such as γ -
20 irradiation, since it was found that the foam structure
21 deteriorated during sterilisation. With the inclusion
22 of the precipitant however, sterilisation of the
23 pad is possible both by γ -irradiation, ethylene oxide
24 sterilisation or other conventional means. This
25 represents a very considerable advantage over the prior (
26 art product.

27
28 The foam sheet is generally produced by foaming the
29 foamable carrier in the presence of the precipitant and
30 allowing the foam to cure, usually by simply exposing
31 the foam to the atmosphere to air dry at ambient
32 temperature. Optionally the foam may be dried at
33 elevated temperatures, for example may be oven dried.
34 Desirably, the cure time of the foam is 40 minutes or
35 less at ambient temperature and preferably the foam
36 cures within 15 minutes, for example within 10 minutes.

1 Where the foam sheet is to be sterilised, it is
2 advantageous to pre-treat the sheet prior to
3 sterilisation in order to further stabilise the sheet.
4 The difficulty with sterilising any foam of the type
5 described is that the foam structure tends to
6 deteriorate and collapse during the sterilisation
7 process. The pre-treatment of the sheet preferably
8 involves impregnating the sheet with further
9 precipitant. Conveniently, this may entail immersing
10 the sheet in a bath of the precipitant or of a solution
11 of the precipitant. For example, the sheet may be
12 immersed in a bath of calcium chloride or calcium
13 citrate. To ensure that the precipitant penetrates
14 into the centre of the foam sheet, the sheet may be
15 gently squeezed whilst immersed in the bath.
16 Generally, immersion of the sheet for a short period of
17 time, such as 2 to 3 minutes, is sufficient. The sheet
18 may then be removed from the bath of precipitant,
19 washed in a mixture of de-ionised water and glycerine
20 to enhance moisture content and then dried. The
21 stabilised foam sheet may then be sterilised by gamma
22 radiation or through use of ethylene oxide.

23
24 The ratio of de-ionised water : glycerine in the wash
25 stage is preferably 19:1 by volume.

26
27 The treated foam sheet is desirably oven dried at
28 relatively low temperatures, for example 100°C or less,
29 preferably approximately 35°C.

30
31 In a preferred embodiment the foamable carrier includes
32 a combination of copper and zinc ions, optionally in
33 the form of water soluble glass(es). We have found
34 that a foam containing appropriate quantities of these
35 metal ions are particularly resistant to the
36 deleterious effects of sterilisation. We hypothesise

1 that the copper and zinc ions act as scavenger of free
2 radicals produced in the foam during sterilisation and
3 which are, we believe, responsible for the breakdown in
4 structure of the foam. Additionally, both copper and
5 zinc ions have a radioprotective effect. Consequently,
6 we consider that any material known for its use as a
7 free radical scavenger and/or as a radioprotectant may
8 likewise exhibit a protective effect on the foam
9 structure during sterilisation.

10

11 Optionally the manufacture of a prefoamed product may
12 envisage a continuous foaming process. The sheet may
13 be divided into a convenient size and may be packaged.
14 Optionally the foam sheet may be produced on contoured
15 surface so that it is moulded to a pre-determined
16 shape.

17

18 Examples of suitable foamable gelling agents for use in
19 the composition of the present invention include (but
20 are not limited to) alginate and derivatives thereof,
21 carboxymethylcellulose and derivatives thereof,
22 collagen, polysaccharides (including, for example,
23 dextran, dextran derivatives, pectin, starch, modified
24 starches such as starches having additional carboxyl
25 and/or carboxamide groups and/or having hydrophillic
26 side-chains, cellulose and derivatives thereof), agar
27 and derivatives thereof (such as agar stabilised with
28 polyacrylamide), carageenan, polyethylene oxides,
29 glycol methacrylates, gelatin, gums such as xanthum,
30 guar, karaya, gellan, arabic, tragacanth and locust
31 bean gum. Also suitable are the salts of the
32 aforementioned carriers, for example, sodium alginate.
33 Mixtures of any of the aforementioned gelling agents
34 may also be used, as required.

35

36 Preferred foamable gelling agents include alginate,

1 carageenan, carboxymethylcellulose, the derivatives and
2 salts thereof and mixtures of any of these. Alginate
3 (the derivatives or salts thereof, such as sodium and
4 calcium alginate) are especially preferred. Foamable
5 gelling agents having a molecular weight of from 10,000
6 to 200,000 kDa are preferred, especially over 100,000
7 kDa, for example 150,000 to 200,000 kDa, may be used.

8
9 The formulation may further comprise a foaming agent,
10 which promotes the formation of the foam. Any agent
11 having a surfactant character may be used. The
12 surfactants may be cationic, non-ionic or anionic.
13 Examples of suitable foaming agents include cetrimide,
14 lecithin, soaps, silicones and the like. Commercially
15 available surfactants such as Tween™ are also suitable.
16 Cetrimide (which additionally has an anti-bacterial
17 activity) is especially preferred.

18
19 The formulation of the present invention (and thus the
20 foam) may be used to deliver pharmaceutically active
21 agents, in particular to deliver such agents in a
22 controlled release manner. Mention may be made of:

23
24 Antiseptics, Antibacterials and Antifungal agents,
25 such as Chlorhexidine, acetic acid, polynoxylin,
26 povidone iodine, mercurochrome phenoxyethanol,
27 acridene, silver nitrate, dyes eg brilliant green,
28 undecanoic acid, silver sulphadiazine, silver
29 proteins and other silver compounds,
30 metronidazole, benzaclonium chloride;

31
32 Nutritional agents, such as vitamins and proteins;

33
34 Growth factors and healing agents, including
35 Ketanserin a serotonomic blocking agent;

36

1 Living Cells;

2

3 Enzymes include streptokinase and streptodormase;

4

5 Elements - zinc, selenium, cerium, copper,
6 manganese, cobalt, boron, arsenic, chromium
7 silver, gold, gallium;

8

9 Charcoal;

10

11 Desloughing and Debriding agents such as
12 hypochlorite and hydrogen peroxide;

13

14 Astringents including potassium permanganate;

15

16 Antibiotics exemplified by neomycin and framycetin
17 sulphate, sulfamylon, fusidic acid, mupirocin,
18 bacitracin, gramicidin.

19

20 In addition the formulation of the present invention
21 may further comprise other conventional additives such
22 as plasticisers and humectants (such as glycerol,
23 propane-1,2-diol, polypropylene glycol and other
24 polyhydric alcohols), free radical scavengers to
25 stabilise against the effects of sterilisation by
26 irradiation, viscosity-adjusting agents, dyes and
27 colorants, and the like.

28

29 Several experiments including comparative tests have
30 been made in order to demonstrate some of the
31 advantages of the new compositions of the invention.
32 Of course the embodiments described hereinbelow are
33 submitted in order to better describe the invention and
34 not to limit its scope.

35

36

1 **EXAMPLE 1**2 **PROCEDURE FOR MANUFACTURE OF UNIT BATCH (100 g) of**
3 **ALGINATE GEL**

4

5 Typically the alginate gels are made according to the
6 following process:

- 7 1. De-ionised (DI) water is measured and poured
8 into mixing vessel 1.
- 9 2. Desired amounts of suitable alginate (for
10 example Keltone or Manucol) and glycerine are
11 weighed using a calibrated balance, reading
12 to 2 decimal places.
- 13 3. Alginate and glycerine are mixed together in a
14 beaker until no lumps remain.
- 15 4. The whole alginate/glycerine mix is added very
16 slowly to the water.
- 17 5. Once all the alginate/glycerine has been added to
18 the water, the mixture is stirred until a smooth
19 gel has formed.

20

21 Several different alginate gels have been made
22 according the above process. They differ and are
23 referred to by the amount of alginate (for example
24 Keltone) used. For example the alginate gel code 6½ has
25 the following composition:

26

27 GEL CODE	6½
28 DI Water	80 ml
29 Glycerine	25.22 g
30 Keltone	6.5 g
31 Unit Batch Wt	111.72 g

32

33 The above composition can be varied to include other

1 weights of alginate, which would be reflected in the
2 gel code number. For example a composition having 8g
3 alginate (plus 80ml DI water and 25.22g glycerine)
4 would be designated gel code 8. Analogous gel codes
5 are used when other gel formers (eg carageenan or CMC)
6 are substituted for the alginate in the above
7 composition.

8
9 In one embodiment, the gelling agent may be present in
10 the form of a suspension, for example a suspension in
11 glycerine. To avoid diluting the gelling agent, the
12 gelling agent suspension may be made up with less
13 glycerine such that the total quantity of glycerine
14 present in the gelling agent mixture and in the
15 precipitant suspension adds up to the required amount.
16 For example, the glycerine in the gelling agent mixture
17 and precipitant suspension may be varied as follows:

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

Glycerine per 80 ml DI water and 6 g alginate (g)	Glycerine in precipitant suspension (g)
25.22	0
23.0	2.22
20.0	5.22
18.22	7.0
15.0	10.22

The above is illustrated with respect to a gel code 6
composition, but the division of glycerine may be made
for other gel code compositions, and is also not
limited to the specific volumes illustrated above.

1 **PROCEDURE FOR FOAM PRODUCTION**

2

3 The propellant used to produce the foam can be
4 compressed gases such as air, nitrogen, nitrous oxide
5 or air, hydrofluorocarbons such HFC134a or 227 or
6 hydrocarbons including propane, isopropane, n-butane,
7 isobutane and 2-methylbutane.

8

9 Propellant vapour pressure can range from 0 to 110 PSIG
10 at 70°C although the preferred range is 20 to 70 PSIG.
11 Values within this range can be achieved for example by
12 blending the three hydrocarbons propane, isobutane and
13 butane. Calor Aerosol Propellants (CAP) sold by Calor
14 Gas Ltd Slough may be used as propellant gas, when a
15 blend of propane, isobutane and butane is used the
16 proportions can be as follows:

17

18	<u>Grade</u>	<u>Propane %</u>	<u>Isobutane %</u>	<u>n Butane%</u>
19	CAP 30	11	29	60
20	CAP 40	22	24	54
21	CAP 70	55	15	30

22

23 A foam according to the invention can advantageously be
24 produced following the following process:

- 25 1. 100 g of a gel according to the invention is
26 poured to an aerosol canister.
- 27 2. 2.5 g of calcium citrate (food grade) is
28 added to the canister.
- 29 3. A valve is crimped onto the canister.
- 30 4. Air is purged from the canister.
- 31 5. 4.5 g of propellant gas is added into the
32 canister (65:35 CAP 40 : Isopentane
33 propellant) and an actuator is positioned on
34 the valve.
- 35 6. The canister is shaken vigorously for 20-30
36 seconds.

1 7. The canister is inverted and the foam dispensed.

2

3 EXAMPLE 2

4 Using a range of water-based gel formulations detailed
5 below tests were done to improve the "setting" time and
6 stability of the gel and its foam.

7

8 Preferred alginate compositions have an amount of
9 alginate ranging from 5-9g in the composition set out
10 in Example 1. Preferred alginates are Keltone HV and
11 Manucol DMF.

12

13 Experiment 1. Gel Code 6% Alginate gel and foam mixed
14 with calcium citrate compared to Gel Code 6% alginate
15 gel alone

16

17 Foamed gel with calcium citrate

18 2.5 g calcium citrate was added to 100 g of gel and the
19 foamed gel was spread out onto plastic sheeting. The
20 resultant foam pad was liftable in 15 minutes.

21

22 Foamed gel without calcium citrate

23 The above experiment was reproduced by foaming the gel
24 on its own as described above. The "setting" time of
25 the foam was 10 hours.

26

27 The experiments were repeated using 100 g unfoamed gel
28 with and without calcium citrate. Similar setting
29 times to those observed for the foamed gels were
30 obtained (15 minutes and 10 hours respectively) before
31 the gel pads were liftable.

32

33 Conclusion: Calcium citrate speeds up and controls the
34 setting time of the gel and the foam.

35

36 Experiment 2. Gel Code 8 Alginate gel mixed with water

1 soluble glass (WSG) containing phosphate and boron
2 compared to gel code 8 alginate gel alone.

3

4 The WSG was comprised as follows:

5 28.5M% CaO

6 3M% Ag

7 5M% B₂O₃

8 18.5M% MgO

9 45M% P₂O₅

10

11 Foamed gel with WSG

12 2.5 g of WSG was mixed with 100 g gel and the foamed
13 mixture was spread out onto plastic sheeting. The
14 resultant foam pad was liftable in 120 mins.

15

16 Foamed gel without WSG

17 The above experiment was repeated by foaming the gel on
18 its own. The "setting" time of the foam was
19 approximately 10 hours.

20

21 The experiments were repeated using 100 g unfoamed gel
22 with and without WSG. Similar setting times to those
23 observed for the foamed gels were obtained (120 minutes
24 and 10 hours respectively) before the gel pads were
25 liftable.

26

27 Conclusion: WSG speeds up and controls the setting
28 time of the gel and the foam.

29

30 Experiment 3. Gel Code 4 Carageenan gel mixed with
31 calcium citrate compared to gel code 4 gel alone

32

33 Foamed gel with calcium citrate

34 3 g of calcium citrate was mixed with 100 g gel and the
35 foamed mix was spread out onto plastic sheeting. The
36 resultant foam pad was liftable in 120 mins.

1 Foamed gel without calcium citrate

2 The above experiment was repeated by foaming gel on its
3 own as described above. The "setting" time of the foam
4 was 10 hours.

5

6 The experiments were repeated using 100 g unfoamed gel
7 with and without calcium citrate. Similar setting
8 times to those observed for the foamed gels were
9 obtained (120 minutes and 10 hours respectively) before
10 the gel pads were liftable.

11

12 Experiment 4. Gel Code 4½ Carageenan gel and gel code
13 6½ alginate gel mixed with calcium citrate compared to
14 gel code 4½ carageenan gel and gel code 6½ alginate gel
15 alone

16

17 Foamed gel with calcium citrate

18 2.5 g of calcium citrate was mixed with (50 g alginate
19 and 50 g carageenan) gel and the foamed mix was spread
20 out onto plastic sheeting. The resultant foam pad was
21 liftable in 15 mins.

22

23 Foamed gel without calcium citrate

24 The above experiment was repeated by foaming the mixed
25 gel on its own. The "setting" time of the foam pad was
26 10 hours.

27

28 The experiments were repeated using 100 g unfoamed gel
29 with and without calcium citrate. Similar setting
30 times to these observed for the foamed gels were
31 obtained (120 minutes and 10 hours respectively) before
32 the gel pads were liftable.

33

34 Experiment 5. Gel Code 6½ Alginate gel mixed with
35 calcium citrate and added bentone IPM gel

36

1 2.5 g calcium citrate was added to 100 g of gel with 1g
2 bentone IPM gel, admixed in an aerosol canister and
3 dispensed therefrom as a foam onto a plastic surface.
4 The resultant foam pad was liftable in 12 minutes.
5 Bentone IPM gel is an admixture of isopropyl myristate,
6 sterealkonium hectorite and propylene carbonate.

7
8 Conclusion: Calcium citrate and bentone gel control
9 the setting time of the foam. Bentone gel also acts as
10 a reological agent and assists in the smoothness of
11 delivery from the can.

12
13 **Experiment 6. Gel Code 6½ Alginate gel mixed with**
14 **calcium citrate and added cetrimide**

15
16 2.5 g calcium citrate was added to 100 g of alginate
17 gel with 1g cetrimide in an aerosol canister and foamed
18 onto a plastic surface. The resultant foam pad was
19 liftable in 15 minutes.

20
21 Conclusion: Calcium citrate speeds up the setting time
22 of the foam. Cetrimide increases the cell structure of
23 the product.

24
25 **Experiment 7. Gel Code 6½ Alginate gel mixed with**
26 **calcium citrate and added Tween 20**

27
28 2.5 g Calcium citrate was added to 100 g of alginate
29 gel with 1g Tween 20 and foamed onto a plastic surface.
30 The resultant foam pad was liftable in 12 minutes.

31
32 Conclusion: Calcium citrate speeds up the setting time
33 of the gel. The additive Tween 20 gave a much smoother
34 delivery and an airier foam. Tween 80, 60 and 40 were
35 also tried and all assisted in the delivery and product
36 cell structure.

1 Experiment 8. Gel Code 4 Carboxymethyl cellulose and gel
2 code 6½ alginate gel mixed with calcium citrate
3 compared to the gel alone

4
5 2.5 g calcium citrate was added to (50 g CMC & 50 g
6 alginate gel) and then the mixture was foamed onto a
7 plastic surface. The resultant foam pad was liftable
8 in 25 minutes. The gel foamed on its own was liftable
9 overnight (approx. 10 hours).

10

11 Experiment 9. Gel Code 4 Carboxymethyl cellulose gel
12 mixed with aluminium chloride compared with the gel
13 alone

14

15 2 g aluminium chloride was mixed with 100 g CMC gel.
16 The gel was spread onto a plastic surface. The
17 resultant gel was liftable instantly. The gel alone was
18 liftable overnight (approx. 10 hours).

19

20 Experiment 10. Gel Code 6 Alginate gel mixed with
21 citric acid compared to gel code 6 alginate gel alone

22

23 2.5 g of citric acid was mixed with 100 g alginate gel
24 and the mix was spread out onto plastic sheeting. The
25 resultant gel pad was liftable in 120 mins. 100 g of
26 the gel alone was spread onto plastic sheeting and the
27 resultant pad was only liftable overnight (approx. 10
28 hours).

29

30

31

32

33

34

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36

1 Experiment 11. Gel Code 6½ Alginate gel was mixed with
2 the following powders on a 100 g gel: 2.5 g powder
3 basis

Powder	Results as a gel	Results as a foam
Calcium Chloride	Gel pad was formed instantly	Fast setting foam
Calcium Sulphate	Gel pad formed reasonably quickly	Foam set reasonably quickly
Aluminium Chloride	Gel pad formed instantly	Fast setting foam
Calcium Metaborate	Gel pad formed instantly	Fast setting foam

13

14

15 Experiment 12. Setting performances of a foam of a gel
16 code 6½ alginate gel as a function of the amounts of
17 calcium citrate.

18

Batch No	Amount of calcium citrate per 100 g gel	Result
DM02 210798	4 g	Not dispensed - set in can
DM03 210798	3 g	Very difficult to dispense. 9½ minutes to set.
DM04 210798	2.5 g	Easier to dispense than above. 18½ minutes to set
DM05 210798	2.25 g	Taking longer to set. 20 minutes.
DM02 200798	2 g	Setting time - 40 minutes

25

26

27

28

1 **Experiment 13. Gel Code 6% alginate gel with calcium**
2 **citrate and isopentane.**

3
4 100g gel code 6% alginate gel was admixed with varying
5 amounts of calcium citrate (2 to 4g), added to
6 isopentane and mixed thoroughly before being spread
7 onto a glass sheet. The isopentane vaporises at
8 ambient temperatures and boils off through the gel
9 leaving a foam pad of similar consistency to those
10 produced by dispersion from an aerosol can. After
11 half-an-hour the foam pads were liftable.

12
13 **EXAMPLE 3**

14
15 **A. Gel code 5 alginate gel mixed with calcium citrate**

16
17 The gel was prepared by mixing together alginate (5g
18 Keltone HV), 20g glycerine and 80ml de-ionised water.
19 5.22g glycerine was then added to 2.5g calcium citrate
20 and a suspension of precipitant was created. The
21 resultant gel and the suspension of precipitant were
22 added to an aerosol can and a valve fitted. The can
23 was purged of air, filled with 4.5g CAP 40 butane,
24 shaken and dispensed. The foam produced was well mixed
25 and set in 15 minutes.

26
27 **B. Gel code 5 alginate gel mixed with calcium citrate**

28
29 Experiment A was repeated using the same weight of
30 Manucol LKX (5g) instead of Keltone HV. The resultant
31 foam set within 12 minutes.

32
33 **C. Gel code 5 alginate gel mixed with calcium citrate**

34
35 The gel was prepared by mixing together alginate (5g
36 Keltone HV), 20g glycerine and 80ml de-ionised water.

1 5.22g glycerine was then added to 2.5g calcium citrate
2 and a suspension of precipitant was created. The
3 resultant gel was added to the bottom can of the two
4 can packaging system (see our co-pending UK Patent
5 Application No 9823029.5) and the suspension or
6 precipitant was added to the top can. The cans were
7 prepared in the usual way. The two can packaging
8 system was activated and the foam was dispensed. The
9 foam produced was well mixed and set in 15 minutes.

10

11 **D. Gel code 5 alginate gel mixed with calcium citrate**

12

13 Experiment C was repeated using the same weight of
14 Manucol LKX instead of Keltone HV. The resultant foam
15 set within 12 minutes.

16

17 The set foam from A, B, C and D were then further
18 processed by first immersing the foam in a solution of
19 2.5% calcium chloride solution for 2 minutes, rinsing
20 in de-ionised water and then finally rinsing in a 1%
21 glycerine solution. The foam pads were then dried in
22 the oven at 35°C and packaged in sterilisable pouches.

23

24 The resultant sterilised pads were compared with can
25 reference 2 below (see Example 4). The foams produced
26 in the two can system had a more even pore size
27 throughout compared to those made in a one can system.
28 Comparing the suspension with the powder/gel mix showed
29 no difference in the structure of the final product.

30

31 **EXAMPLE 4**

32

33 A 1 litre batch of gel code 5 alginate gel was
34 manufactured. Nine bottom cans of a two can packaging
35 system as described in our co-pending UK Patent
36 Application No 9823029.5 were filled with 100g gel in

(

Can Ref	Top Can Component	Ca Chloride Conc.	Glycerine Sol Conc.	Drying Time	Description of Alginate Pad After EtO Sterilisation
1	2.5 g Ca Citrate	1%	1%	8 hrs	Flexible, soft & sponge-like
				16 hrs	Flexible, soft & sponge-like
2	2.5 g Ca Citrate	2.5%	1%	8 hrs	Moist, flexible & sponge-like
				16 hrs	Flexible, soft & sponge-like
3	2.5 g Ca Citrate	5%	1%	8 hrs	Dry pad with limited flexibility
				16 hrs	Dry pad with limited flexibility
4	2.5 g Ca Citrate	2.5%	2%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like
5	2.5 g Ca Citrate	2.5%	2.5%	8 hrs	Moist, flexible, sponge-like pad
				16 hrs	Moist, flexible, sponge-like pad
6	2.5 g Ca Citrate	2.5%	5%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like
7	2 g Ca Citrate 2 g Activated Charcoal	2.5%	5%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like
8	2 g Ca Citrate 2 g Cu/Zn WSG	2.5%	5%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like
9	2.5 g Ca Citrate 2 g Povidone Iodine	2.5%	5%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like

EXAMPLE 5**Experiment A**

A 600 g batch of gel code 5 was made up using Manucol DMF as the gelling agent. This batch was split into six equal parts and inserted into the bottom can of a dual can aerosol system. The top cans were made up containing 1.5 g calcium citrate and varying amounts of alginic acid ($\frac{1}{2}$ g increments from 0 to $2\frac{1}{2}$ g). Once preparation was complete the cans were foamed out simultaneously and the setting time for each foam was recorded.

Can Number	Gel Weight	Calcium Citrate Weight	Alginic Acid Weight	Setting Time
1	100 g	1.5 g	0 g	20 mins
2	100 g	1.5 g	0.5 g	16 mins
3	100 g	1.5 g	1.0 g	14 mins
4	100 g	1.5 g	1.5 g	10 mins
5	100 g	1.5 g	2.0 g	9 mins
6	100 g	1.5 g	2.5 g	8 mins

Experiment B

Three 100 g batches of gel code 5 was made up using Manucol DMF as the gelling agent with alginic acid incorporated (0 g, 1 g and 2 g added). Each batch was filled into bottom cans and top cans were made up containing 1.5 g calcium citrate. Once preparation complete the cans were foamed out simultaneously and the setting times for each can recorded.

1	Can	Gel Weight	Calcium	Alginic	Setting
2	Number		Citrate	Acid	Time
			Weight	Weight	
3	7	100 g	1.5 g	1 g	8 mins
4	8	100 g	1.5 g	2 g	6 mins
5	9	100 g	1.5 g	0 g	20 mins
6					
7					

1 CLAIMS

2

3 1. A physiologically acceptable formulation for
4 " application to a body as a foam, said formulation
5 comprising a foamable gelling agent and a slow-
6 release precipitant therefor, wherein said slow-
7 release precipitant is combined with said gelling
8 agent during the foaming thereof and stabilises
9 the foamed form of the gelling agent.

10

11 2. A formulation as claimed in Claim 1 wherein said
12 precipitant is packaged separately to said gelling
13 agent prior to foaming.

14

15 3. A formulation as claimed in either one of Claims 1
16 and 2 wherein said gelling agent is alginate,
17 carboxymethylcellulose, collagen, a
18 polysaccharide, agar, a polyethylene oxide, a
19 glycol methacrylate, gelatin, a gum, or salts or
20 derivatives of any of these, or mixtures thereof.

21

22 4. A formulation as claimed in Claim 3 wherein said
23 gelling agent is alginate, carboxymethyl-
24 cellulose, carageenan gel, the derivatives or
25 salts thereof, or mixtures thereof.

26

27 5. A formulation as claimed in any one of Claims 1 to
28 4, wherein said gelling agent has a molecular
29 weight of from 10,000 to 200,000 kDa.

30

31 6. A formulation as claimed in any one of Claims 1 to
32 5, wherein said precipitant is a salt of calcium,
33 zinc, copper, silver or aluminium; borates;
34 glyoxal; or amino-formaldehyde pre-condensates

35

36

- 1 7. A formulation as claimed in any one of Claims 1 to
2 6 further containing a foaming agent.
3
- 4 8. A formulation as claimed in Claim 7 wherein said
5 foaming agent is cetrimide, lecithin, a soap,
6 silicone, a surfactant or the like.
7
- 8 9. A formulation as claimed in any one of Claims 1 to
9 8 wherein the gelling agent comprises an alginate
10 gel, a carageenan gel or a carboxymethylcellulose
11 gel and wherein the precipitant is a calcium salt.
12
- 13 10. A formulation as claimed in any one of Claims 1 to
14 8 wherein the gelling agent comprises
15 carboxymethylcellulose gel and wherein the
16 precipitant is an aluminium salt.
17
- 18 11. A formulation as claimed in any one of Claims 1 to
19 10 further comprising an organic acid in an amount
20 of 0.5 g to 5.0 g per 100 g gelling agent.
21
- 22 12. A physiologically acceptable foam comprising a
23 foamed gelling agent stabilised by a precipitant.
24
- 25 13. The foam as claimed in Claim 12 in the form of a
26 cured foam sheet.
27
- 28 14. A foam as claimed in Claim 12 wherein said
29 precipitant is packaged separately to said gelling
30 agent prior to foaming.
31
- 32 15. A foam as claimed in any one of Claims 12 to 14
33 wherein said gelling agent is alginate,
34 carboxymethylcellulose, collagen, a
35 polysaccharide, agar, a polyethylene oxide, a
36 glycol methacrylate, gelatin, a gum, or salts or

- 1 derivatives of any of these, or mixtures thereof.
2
- 3 16. A foam as claimed in Claim 15 wherein said gelling
4 agent is alginate, carboxymethyl- cellulose,
5 carageenan gel, the derivatives or salts thereof,
6 or mixtures thereof.
7
- 8 17. A foam as claimed in any one of Claims 12 to 16,
9 wherein said gelling agent has a molecular weight
10 of from 10,000 to 200,000 kDa.
11
- 12 18. A foam as claimed in any one of Claims 12 to 17,
13 wherein said precipitant is a salt of calcium,
14 zinc, copper, silver or aluminium; borates;
15 glyoxal; or amino-formaldehyde pre-condensates
16
- 17 19. A foam as claimed in any one of Claims 12 to 18
18 further containing a foaming agent.
19
- 20 20. A foam as claimed in Claim 19 wherein said foaming
21 agent is cetrimide, lecithin, a soap, silicone, a
22 surfactant or the like.
23
- 24 21. A process of sterilising a foam for medical or
25 veterinary use, said process comprising:
26
- 27 a) foaming a formulation of Claims 1 to 11 and
28 allowing said foamed formulation to cure;
29
- 30 b) treating said foam with precipitant;
31
- 32 c) optionally, washing said treated foam;
33
- 34 d) drying said treated form; and
35
36

- 1 e) sterilising said dried foam by exposure to γ -
2 irradiation or ethylene oxide.
3
- 4 22. The process of Claim 21 wherein said treated foam
5 is washed in a de-ionised water/glycerine mixture
6 prior to drying.
7
- 8 23. The process of either one of Claims 21 and 22
9 wherein the treated foam is oven dried at
10 temperatures below 100°C.
11
- 12 24. The process of any one of Claims 21 to 23 wherein
13 the foam is immersed in a bath of calcium chloride
14 or calcium citrate solution as precipitant.
15